Published in final edited form as:

Am J Hum Biol. 2013 ; 25(4): 465–472. doi:10.1002/ajhb.22381.

Association of Height and Pubertal Timing with Lipoprotein Subclass Profile: Exploring the Role of Genetic and Environmental Effects

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Abstract

Objectives—Little is known about the relationship between growth and lipoprotein profile. We aimed to analyze common genetic and environmental factors in the association of height from late childhood to adulthood and pubertal timing with serum lipid and lipoprotein subclass profile.

Methods—A longitudinal cohort of Finnish twin pairs (FinnTwin12) was analyzed using self-reported height at 11–12, 14, 17 years and measured stature at adult age (21–24 years). Data were available for 719 individual twins including 298 complete pairs. Serum lipids and lipoprotein subclasses were measured by proton nuclear magnetic resonance spectroscopy. Multivariate variance component models for twin data were fitted. Cholesky decomposition was used to partition the phenotypic covariation among traits into additive genetic and unique environmental correlations.

Results—In men, the strongest associations for both adult height and puberty were observed with total cholesterol, low-density lipoprotein cholesterol, intermediate-density lipoprotein cholesterol, and low-density lipoprotein particle subclasses (max. $r = -0.19$). In women, the magnitude of the correlations was weaker (max. $r = -0.13$). Few associations were detected between height during adolescence and adult lipid profile. Early onset of puberty was related to an adverse lipid profile, but delayed pubertal development in girls was associated with an unfavorable profile, as well. All

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associations were mediated mainly by additive genetic factors, but unique environmental effects cannot be disregarded.

Conclusions—Early puberty and shorter adult height relate to higher concentrations of atherogenic lipids and lipoprotein particles in early adulthood. Common genetic effects behind these phenotypes substantially contribute to the observed associations.

Height is an important trait defining human morphology, and is determined by the genetic background, nutrition, and other life conditions during childhood and adolescence (Batty et al., 2009; Silventoinen et al., 2003). Adult stature has also shown to be affected by pubertal timing both in men and in women (Biro et al., 2001; Silventoinen et al., 2008).

Accumulating evidence suggests that both height and timing of puberty are related to the lipid profile. Short stature in childhood and adulthood is associated with higher levels of total cholesterol (total-C) and low-density lipoprotein cholesterol (LDL-C), whereas its relationship with high-density lipoprotein cholesterol (HDL-C) and triglycerides is more divergent (Benetou et al., 2006; Fujita et al., 2011; Henriksson et al., 2001; Kouda et al., 2003; La Batide-Alanore et al., 2003; Orchard et al., 1980; Ranasinghe et al., 2011).

Similarly, early pubertal timing has been related generally to an unfavorable lipid profile (Feng et al., 2008; Frontini et al., 2003; Widen et al., 2012). However, the biological mechanisms of these associations are poorly understood. Several studies have demonstrated that height, pubertal timing, and multiple metabolites are quite highly heritable (Benyamin et al., 2007; Jelenkovic et al., 2011; Kettunen et al., 2012; Silventoinen et al., 2003; Wehkalampi et al., 2008), but to our knowledge, no study has utilized a multivariate genetic analysis to analyze the relationship of height and puberty with lipid profile. Therefore, whether these associations are attributable to genetic factors remain largely unknown.

Circulating metabolites have key roles in numerous biological pathways. Until recently, the search for metabolic risk factors had focused on only relatively few metabolites, but recent investigations suggest that alternative lipoprotein measures may improve risk prediction (Bertram et al., 2009; Chasman et al., 2009; Tukiainen et al., 2012). This is relevant because alterations in lipid and lipoprotein levels represent one of the major risk factors for coronary heart disease (CHD) (Kuulasmaa et al., 2000; Levy, 1987), which in turn has been inversely associated with height during childhood and adolescence (Silventoinen et al., 2012), pubertal timing (Lakshman et al., 2009), and adult height (Paajanen et al., 2010). The concentration of distinct lipoprotein subclasses, as well as the average particle size, can be measured by nuclear magnetic resonance (NMR) spectroscopy (Ala-Korpela, 2008; Ala-Korpela et al., 2009; Jeyarajah et al., 2006).

As the association between adult height and lipid profile is shaped over the life course, detailed knowledge of links with critical developmental events may highlight important biological mechanisms. Major limitations of existing studies include the restriction of the analyses to basic serum lipids and the lack of exploration of common genetic and environmental factors between growth and lipid profile. Our data offer us an opportunity to analyze the association of height and puberty with a large set of serum lipids and lipoproteins in a population-based longitudinal sample of Finnish twins. Accordingly, the specific aims of this study are as follows: (1) to assess the relationship between height and

lipid profile in young adulthood, (2) to ascertain whether this association is owing to common genetic and/or environmental factors, (3) to analyze the effect of earlier physical development (height during adolescence and pubertal timing) on the lipid profile later in life, and (4) to explore possible sex differences in these associations.

MATERIALS AND METHODS

Data sources

The data were derived from the FinnTwin12 study, described in detail elsewhere (Kaprio et al., 2002). This cohort includes five consecutive birth cohorts of Finnish twins (2,600 families with twins) born in 1983–1987. Questionnaires were used to collect data on height at ages 11–12 (mean age: 11.4 years), 14, 17.5 years, and adult age (19–24 years), and pubertal development scale (PDS). Zygosity was determined by well-validated items on physical similarity during school age. DNA analysis confirmed questionnaire assignment of zygosity in 97% of these same-sex adolescent Finnish twins ($n = 395$ pairs). During the fourth wave of the data collection (years, 2006–2009), 780 of these young adult twins visited the study clinic and gave a blood sample for the NMR spectroscopy analysis, and their height and weight were measured. Self-reported height from a questionnaire filled out at home prior to the clinic visit was found to be highly correlated with measured height ($r = 0.99$, $N = 797$). The exclusion criteria for this study were lipid-lowering medication, pregnancy, and missing NMR data, which left 719 participants available for the analyses. Finally, our sample included 298 complete twin pairs: 123 monozygotic (MZ) (46 brother–brother, and 77 sister–sister), 98 same-sex dizygotic (DZ) (47 male and 51 female), and 77 opposite-sex dizygotic pairs. Data collection and analysis were approved by the ethics committee of the Department of Public Health of the University of Helsinki and the Institutional Review Board (IRB) of Indiana University. Written informed consent was obtained from all participants.

Assessment of pubertal timing

Pubertal timing was estimated from PDS score and pubertal height growth. The five-item PDS questionnaire is described in detail elsewhere (Dick et al., 2001; Petersen et al., 1983). PDS score is large for early maturers and small for late maturers. Pubertal timing based on pubertal height growth was assessed using a previously evaluated quantitative estimate of the timing of the pubertal height growth spurt (Wehkalampi et al., 2008). At age when height growth peaks in the general population, relative height (height SD) is influenced by pubertal timing, as well as by genetic height potential (Tanner et al., 1976). By calculating the difference between height SD at pubertal peak height velocity (phv) age and at adulthood, the influence of genetic height potential can be excluded. Therefore, the change in height SDs between these ages reflects timing of puberty (HD:SDS). The age of 12 in girls and 14 in boys represent ages of phv in the general population (Tanner et al., 1976). In this study, height SD at age 11–12 and 14 years was subtracted from height SD at adult age creating the difference: HD:SDS12 and HD:SDS14.

NMR-derived serum lipids and lipoprotein subclass profile

Serum lipid and lipoprotein subclass concentrations were measured by proton NMR spectroscopy as described previously in detail (Soininen et al., 2009; Tukiainen et al., 2012). This NMR platform has been recently applied in various extensive epidemiological and genetic studies (Chambers et al., 2011; Inouye et al., 2010; Kettunen et al., 2012). In this study, concentrations of the lipoprotein subclasses were grouped in three subclasses (large, medium, and small) of HDL, LDL, and very lowdensity lipoprotein (VLDL) (Table 1). The mean particle size for HDL, LDL, and VLDL particles was calculated by weighting the corresponding subclass diameters with their particle concentrations. Intermediate-density lipoprotein (IDL) particles were included in the LDL measure. Apolipoprotein B (apoB) and apolipoprotein A-1 (apoA-1) were estimated from an extended version of the Friedewald formula (Niemi et al., 2009).

Statistical methods

We conducted the statistical analyses using the Stata statistical software package (release 12.0; Stata, College Station, TX). As NMR-derived particle concentrations were not normally distributed, logarithmic transformation was applied to these variables. Height, pubertal timing, and metabolite values were adjusted for age by linear regression model, including sex as a covariate. In the analyses where twins were treated as individuals, the standard errors were corrected for clustering of twin pairs by survey methods (Rao and Scott, 1984). The resulting residuals were used as input phenotypes for the following analyses. Principal component analysis was used to determine the number of principal components that explain most part of the variance of the studied lipids and lipoproteins. As the strong correlation among these metabolites makes the traditional Bonferroni correction for multiple testing too conservative, the number of principal components provides a more permissive *P*-value threshold. In this study, the first five principal components explained more than 97% of the variance, allowing associations to be significant at $P < 0.01$ after the Bonferroni correction.

In genetic analyses, we used quantitative genetic modeling for twin and family data (Neale and Cardon, 2003). Briefly, the analysis is based on the fact that MZ twins share the same gene sequence, whereas DZ twins share, on average, 50% of their genes identical-by-descent. Variance of a trait can be partitioned into additive genetic effects (A: correlated 1.0 for MZ and 0.5 for DZ pairs), common (shared) environmental effects (C: by definition, correlated 1.0 for all pairs), unique (nonshared) environmental effects (E: by definition, uncorrelated in all pairs), and dominance effects (D: 1.0 for MZ and 0.25 for DZ pairs). As pubertal timing and growth differ between sexes, we did not test whether the same sets of genes influence the variation of height in boys and girls and we present parameter estimates for each sex separately. This decision was also based on our previous results which showed that parameters estimated for height during adolescence could not be set equal between males and females in this cohort (Jelenkovic et al., 2011). The genetic models were carried out by the Mx statistical package (Neale, 2003) for each phenotype. We continued the analyses by studying the associations of height and pubertal timing with lipid profile using multivariate correlation model based on reparametrization of Cholesky decomposition. This procedure decomposes the variation and covariation in the data into a series of uncorrelated

genetic and environmental factors. According to this model, the trait correlation between two phenotypes is owing to additive genetic correlation (r_A), indicating the same or closely linked genes, and unique environmental correlation (r_E), indicating the same or correlated environmental factors unique to each twin individual.

RESULTS

Characteristics of the participants

The characteristics of the sample are summarized separately by sex in Table 1. Mean values for height were expectedly higher in boys than in girls over the study period; only at 11–12 years girls were slightly taller. Men also presented a significantly greater weight and body mass index (BMI) than women at adult age. As expected, the PDS score was greater for females both at 11–12 and at 14 years of age. Women had generally a more favorable lipid profile than men characterized by higher HDL-C, increased HDL-C/LDL-C, larger HDL and LDL particle size, higher HDL particles concentration, higher apoA-1, and a lower apoB/apoA-1 ratio. However, women had higher total-C, IDL-C, and LDL particle concentration.

Association between height and lipid profile

The number and magnitude of significant phenotypic correlations between adult height and lipid profile was greater for men than for women (Table 2). Taller individuals tend to present lower levels of serum lipids and lipoproteins than shorter individuals. As very small changes were detected when additionally adjusted for BMI (Supporting Information Table 1), changes that were nonexistent in women, we consider that the nonadjusted correlations offer greater clarity in interpreting the data. Very few correlations were consistent between height during growth and lipid profile in young adulthood (Supporting Information Table 2). Among men, stature at 17 years was inversely associated with medium HDL and apoA-1, whereas shorter women tended to have a worse lipid profile. No evidence for C or D effect was found in this study (data not shown). Accordingly, we chose to use the additive/specific environmental (AE) model for all phenotypes in further multivariate analyses. Genetic correlations followed the pattern of phenotypic ones, but specific environmental correlations between height and lipid profile were nonsignificant (Table 2 and Supporting Information Table 2).

Associations between pubertal timing and lipid profile

None of the correlations was significant for PDS at 11–12 years (max. $r = 0.07$). For PDS14, only those that are significantly associated are presented (Table 3). Although detectable only in females, correlations between PDS14 and HDL variables were positive, suggesting that very late puberty was related to an unfavorable HDL particle profile; this was confirmed by the results from HD:SDS14 (Table 4). HD:SDS12 was inversely associated with small LDL in females and with several unfavorable serum lipids and lipoproteins in males.

DISCUSSION

In this longitudinal population-based twin study, detailed information is provided on the relationship of height and pubertal timing with lipid profile. We report several associations

that have not been described before, as well as novel findings on the genetic background determining these relationships. The results highlight that being taller is associated with the propensity to have lower concentrations of atherogenic lipids and lipoproteins. Similarly, early onset of puberty is related to an overall adverse lipid profile, but a delayed puberty can also have unfavorable effects. The revealed associations are mainly mediated by genetic factors although unique environmental factors shared by traits cannot be disregarded.

The general pattern across populations (Bertram et al., 2009; La Batide-Alanore et al., 2003; Pierce et al., 2010; Widen et al., 2012) in determining a more favorable lipid profile in women than in men was observed in our analyses, as well. It has been suggested that the significantly higher HDL-C content in females could be owing to a higher lipid synthesis (Bertram et al., 2009). In this study of Finnish young adult twins, height and puberty were more closely related to the studied lipid and lipoprotein levels in males than in females, which justifies analyzing these relationships separately by sex. The small change observed in the associations when additionally adjusted for BMI is in agreement with the findings of Henriksson et al. (2001), and may be explained by the correlation of height with BMI (0.12 and 0.05 in men and women, respectively). That is, the adjustment for BMI, which is positively correlated with a worse lipid profile, would be increasing the associations between height and unfavorable lipids.

According to the research literature, taller children and adults tend to have lower total-C and LDL-C content but the pattern is not so well established for HDL-C, for which associations vary from nonsignificant to negative and positive (Benetou et al., 2006; Fujita et al., 2011; Gunnell et al., 2003; Henriksson et al., 2001; Kouda et al., 2003; La Batide-Alanore et al., 2003; Orchard et al., 1980; Ranasinghe et al., 2011). It has been reported that LDL-C concentration tracks better from childhood to adulthood than do HDL-C levels (Uiterwaal et al., 1997; Webber et al., 1991), suggesting that HDL-C level could be affected by additional sources of variability, especially during the pubertal stage where a change in central pattern of body fat occurs (van Lenthe et al., 1998). The relationship of height with triglycerides has been less studied, and the results are divergent (La Batide-Alanore et al., 2003; Orchard et al., 1980; Ranasinghe et al., 2011).

Concerning lipoprotein subclasses, the pattern for large HDL is very similar to HDL-C in our sample. This is consistent with the findings of Mora et al. (2009), who reported a high correlation between HDL-C and large HDL in comparison to that with small and medium HDL, and thus suggesting that the potentially protective effects of HDL-C may be owing to the large HDL particles. The strongest (negative) associations between adult height and lipoproteins were found for LDL particles in both sexes. Recent studies have suggested that LDL particle concentration is a significant predictor of future CHD risk (El Harchaoui et al., 2007; Mora et al., 2009) and that CVD risk may be more closely related to atherogenic lipoprotein particle concentration than to LDL-C (Barter et al., 2006). In the study of Mora et al. (2009), HDL and VLDL particle sizes were significantly correlated (inversely and directly, respectively) with CVD even after adjustment for the respective concentrations; however, we observed only a significant association between HDL particle size and PDS14 in women.

Earlier developing boys had more adverse lipid and lipoprotein levels. In women, pubertal timing (at 11–12 years) correlated only with small LDL particle concentration, which has been associated with more than a threefold increase in the risk of CHD (Lamarche et al., 1999). In contrast to the findings from the Northern Finland Birth Cohort 1966 (Widen et al., 2012), in which an inverse relationship was found between puberty and HDL-C both in men and in women at the age of 31 years, associations with “good” lipids levels were not significant in our study. These authors also observed that triglycerides in men remain significant after adjustment for several covariates (Widen et al., 2012); however, Pierce et al. (2010) reported that the association between pubertal timing and lipids was completely explained by BMI or waist circumference. A noteworthy finding of this study is the consistent inverse association between pubertal development at 14 years (both HD:SDS14 and PDS14) and a favorable lipid profile in women. As pubertal development is normatively in an advanced stage at 14 years in girls, these results suggest that very late puberty is related to an unfavorable lipid profile.

Our results showed that the associations of height and pubertal timing with the lipid profile are explained to a great extent by pleiotropic effects, that is, genes acting to increase the value of one trait also increase (positive association) or decrease (negative association) the magnitude of the other. It is important to note that in the previous studies (Jelenkovic et al., 2011; Kettunen et al., 2012; Wehkalampi et al., 2008) the effect of the common environmental component was much smaller than that of the genetic component, and thus even if it exists, the associations appear to be mainly because of common genetic factors. Common genetic factors between height and lipid profile could be supporting the hypothesis of “thrifty genotype” (Neel, 1962). Based on this hypothesis, some genes could prompt the body to store up fat for later times of starvation and therefore were, advantageous in times of alternating food abundance and scarcity. Thus, if height is inversely related to serum lipid and lipoprotein concentration, we can speculate that natural selection might have led to shorter individuals, who would have higher probability to survive until the reproductive age because they need to use less energy for growth. However, it should be mentioned that there is not necessarily any association between total energy intake and serum lipid levels. For example, it has been observed that total-C and LDL-C concentrations are higher in subjects with an apolipoprotein E (apoE) e4 allele (Bennet et al., 2007; Mahley et al., 2000; Ordovas, 1999) and, in turn, e4 allele frequencies follow a curvilinear relationship with absolute latitude (Eisenberg et al., 2010). As mean stature is greater in northern than in southern part of Europe, apoE e4 allele frequency is related to height, but to our knowledge apoE is not a height gene. However, other height genes have shown to be associated with lipid metabolism. That is, genome-wide association studies confirmed that NCAPG/LCORN locus has an effect on human height (Gudbjartsson et al., 2008; Weedon et al., 2008) and that NCAPG 1442M mutation is related to postnatal growth (especially with the onset of puberty) and lipid deposition in bovine cattle (Weikard et al., 2010). Therefore, similar physiological mechanisms seem to operate in different mammalian species. Finally, the influence of unique environmental factors on the relationship of height at 11.5 years with HDL-C and total HDL in boys might be owing to the effect of nutrition before puberty, that is, favorable nutrition would result in taller individuals with a better lipid profile. To our knowledge, no study has focused on common genetic and environmental factors between

pubertal timing and lipid profile, and the scarce data available for height were inconsistent (Bastarrachea et al., 2007; Butte et al., 2006); that is, height showed negative genetic correlation with total-C and HDL-C (-0.33 and -0.27 , respectively) in childhood (Butte et al., 2006) and nonsignificant with total-C and total-TG in adulthood (Bastarrachea et al., 2007).

Our study has several strengths. It is unique in that it provides comprehensive information on the pleiotropic effects determining the relationship of height and puberty with a detailed lipid profile in males and females. The four measures of height available from this longitudinal study allow us also to detect the changes in these associations during the growth process. Furthermore, we have information on puberty measured by PDS at two time points in both sexes. But our study has potential limitations, as well. The main limitation of the study is our relatively small sample size, creating challenges in evaluating statistical significance for some of the associations of interest. Reliance on self-estimated assessments (height at 11–12, 14, and 17 years) may cause some inaccuracy, but self-reported final height was highly correlated with measured height. Finally, another limitation is the issue of multiple testing, with potentially false-positive associations among the correlations evaluated. Although the Bonferroni correction based on the principal components showed a more permissive threshold ($P < 0.01$) than the traditional correction, we still believe that associations with $P < 0.05$ cannot be disregarded because many related lipids and lipoproteins showed the same trend and thus provide considerable robustness to the study. However, these results need to be replicated in other cohorts.

CONCLUSIONS

To summarize, adult height and pubertal timing are related to several serum lipids and lipoproteins in young adulthood, both in males and in females. Although unique environmental factors shared by traits cannot be disregarded, these associations are in great part determined by common genetic factors. Shorter stature, early pubertal timing in boys, and delayed puberty in girls are associated with a worse lipid profile. Despite the relative small magnitude, the pattern of these associations is consistent. Thus, both being shorter and develop early/very late might be considered as risk factors for adult lipid abnormalities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Contract grant sponsor: The Basque Government's Department of Education, Universities and Research (DEUI), Doctoral Programs of Public Health, The Juho Vainio, Yrjö Jahansson, Kone, Biomedicum Helsinki Foundations. Contract grant sponsor: National Institute of Alcohol Abuse and Alcoholism; Contract grant numbers: AA12502; AA00145; AA09203; Contract grant sponsor: The Academy of Finland; Contract grant numbers: 205585; 141054; Contract grant sponsor: The Academy of Finland; Contract grant number: 137870; Contract grant sponsor: The Research Programme of the Academy of Finland Responding to Public Health Challenges; Contract grant number: 129429; Contract grant sponsors: The Jenny and Antti Wihuri Foundation, The Finnish Foundation for Cardiovascular Research, The Strategic Research Funding from the University of Oulu.

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TABLE 1

Basic descriptive statistics of anthropometric, pubertal timing, and metabolic characteristics by sex^a

	Males (n = 314)		Females (n = 405)	
	Mean	SD	Mean	SD
Adult age (years)	22.43	0.70	22.32	0.56
Height at adult age (cm)	179.58	7.01	166.14	6.38
Weight at adult age (kg)	77.31	14.66	63.29	12.55
BMI at adult age	23.90	3.75	22.88	4.03
Height at 11–12 years (cm)	147.03	7.48	147.64	7.50
Height at 14 years (cm)	164.24	9.39	162.02	6.43
Height at 17 years (cm)	178.53	7.05	165.53	6.18
PDS at 12 years	1.31	0.27	1.69	0.42
PDS at 14 years	2.02	0.50	2.84	0.55
<i>Plasma lipids (mmol/L)</i>				
Total-C	4.45	0.79	4.85	0.86
HDL-C	1.58	0.30	2.01	0.43
LDL-C	1.70	0.50	1.65	0.45
HDL-C/LDL-C	1.02	0.36	1.30	0.44
IDL-C	0.65	0.15	0.68	0.15
Triglycerides	1.01	0.46	1.00	0.45
<i>Lipoprotein particle size (nm)</i>				
HDL particle size	9.84	0.21	10.11	0.24
LDL particle size	23.57	0.16	23.63	0.17
VLDL particle size	36.68	1.35	36.26	1.39
<i>HDL particle concentration (μmol/L)</i>				
Small HDL	4.66	0.38	4.80	0.54
Medium HDL	2.01	0.33	2.43	0.46
Large HDL	1.27	0.52	2.08	0.77
Total HDL	7.94	0.90	9.31	1.38
<i>LDL particle concentration (nmol/L)</i>				
Small LDL	127.83	34.57	130.23	32.54
Medium LDL	114.88	31.22	113.97	28.77
Large LDL	222.25	55.10	233.39	54.89
Total LDL	464.96	119.24	477.59	113.86
<i>VLDL particle concentration (nmol/L)</i>				
Small VLDL	49.59	16.32	49.43	17.05
Medium VLDL	13.42	7.99	11.97	7.32
Large VLDL	3.64	3.45	3.33	3.27
Total VLDL	66.64	26.29	64.74	25.54
<i>Apolipoproteins (g/L)</i>				
Apolipoprotein A1	1.62	0.22	1.86	0.23

	Males (n = 314)		Females (n = 405)	
	Mean	SD	Mean	SD
Apolipoprotein B	0.81	0.19	0.81	0.17
ApoB/ApoA-1	0.51	0.13	0.44	0.10

^aSD, standard deviation; small HDL (8.7 nm); medium HDL (10.9 nm); “large HDL” (very large HDL [14.3 nm] + large HDL [12.1 nm]); small LDL (18.7); medium LDL (23.0 nm); “large LDL” (large LDL [25.5 nm] + IDL [28.6 nm]); “small VLDL” (small VLDL [36.8 nm] + very small VLDL [31.3 nm]); medium VLDL (44.5 nm); “large VLDL” (chylomicrons and extremely large VLDL particles [with particle diameters from ~75 nm upwards] + very large VLDL [mean particle diameter of 64.0 nm] + large VLDL [53.6 nm]).

TABLE 2

Phenotypic, genetic, and environmental correlations between adult height and lipid profile^a

	Males			Females		
	r_P	r_A (CI)	r_E (CI)	r_P	r_A (CI)	r_E (CI)
<i>Serum lipids</i>						
Total-C	-0.18^c	-0.21 (-0.38,-0.05)	0.13 (-0.15,0.40)	-0.07	-0.12 (-0.28,0.04)	0.03 (-0.19,0.24)
HDL-C	-0.12	-0.12 (-0.28,0.03)	0.17 (-0.10,0.43)	0.03	0.00 (-0.15,0.16)	0.04 (-0.18,0.26)
LDL-C	-0.17^c	-0.18 (-0.33,-0.01)	-0.02 (-0.30,0.26)	-0.11^b	-0.17 (-0.32,-0.01)	-0.02 (-0.24,0.20)
HDL-C/LDL-C	0.07	0.06 (-0.09,0.22)	0.13 (-0.15,0.39)	0.11^b	0.13 (-0.02,0.28)	0.04 (-0.18,0.26)
IDL-C	-0.18^c	-0.21 (-0.38,-0.04)	0.10 (-0.19,0.38)	-0.12^b	-0.19 (-0.34,-0.03)	0.05 (-0.18,0.26)
Triglycerides	-0.03	-0.04 (-0.21,0.12)	-0.05 (-0.33,0.23)	-0.06	-0.11 (-0.27,0.05)	0.02 (-0.20,0.23)
<i>Lipoprotein particle size</i>						
HDL particle size	-0.05	-0.05 (-0.21,0.11)	0.10 (-0.18,0.36)	0.07	0.06 (-0.09,0.20)	-0.02 (-0.24,0.20)
LDL particle size	-0.01	-0.06 (-0.31,0.16)	0.08 (-0.21,0.35)	-0.07	-0.11 (-0.29,0.08)	0.05 (-0.17,0.25)
VLDL particle size	0.06	0.07 (-0.10,0.25)	-0.04 (-0.31,0.24)	0.03	0.02 (-0.15,0.19)	0.05 (-0.16,0.27)
<i>HDL particle concentration</i>						
Small HDL	-0.13^b	-0.15 (-0.33,0.02)	0.14 (-0.17,0.42)	-0.07	-0.12 (-0.28,0.04)	0.07 (-0.15,0.28)
Medium HDL	-0.15^b	-0.21 (-0.38,-0.04)	0.17 (-0.11,0.42)	-0.06	-0.13 (-0.29,0.04)	0.11 (-0.11,0.32)
Large HDL	-0.09	-0.09 (-0.25,0.07)	0.08 (-0.20,0.34)	0.04	0.02 (-0.14,0.17)	0.02 (-0.20,0.24)
Total HDL	-0.14^b	-0.17 (-0.33,-0.01)	0.19 (-0.09,0.44)	-0.01	-0.06 (-0.22,0.10)	-0.06 (-0.16,0.27)
<i>LDL particle concentration</i>						
Small LDL	-0.17^c	-0.18 (-0.33,-0.02)	-0.01 (-0.28,0.27)	-0.10	-0.16 (-0.32,0.00)	-0.02 (-0.24,0.20)
Medium LDL	-0.17^c	-0.17 (-0.33,-0.01)	-0.03 (-0.31,0.25)	-0.11^b	-0.17 (-0.32,-0.01)	-0.03 (-0.25,0.19)
Large LDL	-0.19^c	-0.21 (-0.36,-0.05)	0.03 (-0.25,0.31)	-0.13^c	-0.21 (-0.36,-0.05)	0.00 (-0.22,0.22)
Total LDL	-0.18^c	-0.19 (-0.35,-0.04)	0.00 (-0.28,0.28)	-0.12^b	-0.19 (-0.34,-0.03)	-0.01 (-0.23,0.21)
<i>VLDL particle concentration</i>						
Small VLDL	-0.07	-0.11 (-0.27,0.05)	-0.02 (-0.30,0.26)	-0.10	-0.15 (-0.31,0.01)	0.01 (-0.21,0.23)
Medium VLDL	0.01	-0.00 (-0.17,0.17)	-0.05 (-0.32,0.23)	-0.03	-0.06 (-0.23,0.11)	0.06 (-0.16,0.27)
Large VLDL	0.03	0.03 (-0.16,0.23)	-0.02 (-0.40,0.38)	-0.03	-0.08 (-0.26,0.10)	0.06 (-0.17,0.29)

	Males			Females		
	r_P	r_A (CI)	r_E (CI)	r_P	r_A (CI)	r_E (CI)
Total VLDL	-0.04	-0.07 (-0.23,0.09)	-0.02 (-0.30,0.26)	-0.08	-0.12 (-0.28,0.04)	0.02 (-0.20,0.24)
<i>Apolipoproteins</i>						
Apolipoprotein A1	-0.17^c	-0.20 (-0.36,-0.04)	0.16 (-0.11,0.42)	0.02	-0.00 (-0.18,0.18)	0.00 (-0.24,0.24)
Apolipoprotein B	-0.09	-0.12 (-0.28,0.04)	0.08 (-0.20,0.36)	-0.09	-0.11 (-0.27,0.05)	-0.02 (-0.25,0.22)
ApoB/ApoA-1	0.01	-0.01 (-0.16,0.15)	-0.03 (-0.31,0.24)	-0.11	-0.11 (-0.26,0.05)	-0.03 (-0.26,0.21)

^aPhenotypic correlations (r_P) were estimated using Pearson's correlation method. Genetic (r_A) and environmental (r_E) correlations between height and each of the analyzed lipids and lipoproteins were obtained from the multivariate Cholesky model, which decomposes phenotypic covariation into uncorrelated genetic and environmental factors. In each multivariate model, five phenotypes were included: height at 11–12, 14, and 17 years and young adulthood, and one lipoprotein. CI, 95% confidence interval for r_A and r_E .

^b $P<0.05$

^c $P<0.01$.

TABLE 3

Phenotypic, genetic, and environmental correlations between PDS at 14 years and lipid profile^a

	Males			Females		
	<i>r_P</i>	<i>r_A</i> (CI)	<i>r_E</i> (CI)	<i>r_P</i>	<i>r_A</i> (CI)	<i>r_E</i> (CI)
HDL-C	-0.01	-0.09 (-0.32,0.11)	0.22 (-0.08,0.48)	0.20^d	0.17 (-0.09,0.42)	0.21 (-0.04,0.43)
HDL-C/LDL-C	-0.07	-0.18 (-0.39,0.02)	0.36 (0.09,0.57)	0.19^d	0.16 (-0.06,0.36)	0.16 (-0.07,0.37)
HDL particle size	0.01	0.01 (-0.18,0.20)	0.16 (-0.11,0.41)	0.21^d	0.18 (-0.01,0.37)	0.23 (0.01,0.43)
Medium HDL	-0.07	-0.03 (-0.30,0.23)	0.02 (-0.26,0.29)	0.13^b	0.34 (0.06,0.65)	-0.02 (-0.24,0.21)
Large HDL	0.01	-0.04 (-1.00,0.20)	0.17 (-0.16,0.79)	0.20^d	0.39 (0.04,1.00)	0.04 (-0.51,0.32)
Total HDL	-0.05	-0.15 (-0.41,0.08)	0.17 (-0.13,0.44)	0.18^d	0.22 (-0.07,0.53)	0.12 (-0.13,0.35)
Apolipoprotein A1	-0.01	-0.06 (-0.28,0.16)	0.07 (-0.22,0.35)	0.11^b	0.08 (-0.26,0.44)	0.11 (-0.14,0.35)
ApoB/ApoA-1	0.03	0.19 (-0.02,0.44)	-0.36 (-0.60,-0.07)	-0.16^c	0.03 (-0.29,0.24)	-0.19 (-0.42,0.07)

^aPhenotypic correlations (*r_P*) were estimated using Pearson's correlation method. Genetic (*r_A*) and environmental (*r_E*) correlations between pubertal timing and each of the analyzed lipids and lipoproteins were obtained from the multivariate Cholesky model, which decomposes phenotypic covariation into uncorrelated genetic and environmental factors. In each multivariate model, two phenotypes were included: PDS14 and one lipoprotein. CI, 95% confidence interval for *r_A* and *r_E*.

^b*p* < 0.05

^c*p* < 0.01

^d*p* < 0.001.

TABLE 4

Phenotypic, genetic, and environmental correlations of HD:SDS12 and HD:SDS14 with lipid profile^a

	Males			Females		
	r_P	r_A (CI)	r_E (CI)	r_P	r_A (CI)	r_E (CI)
Total-C						
HD:SDS12	-0.19^d	-0.27 (-0.44,-0.10)	0.04 (-0.25,0.32)	-0.03	-0.09 (-0.25,0.08)	-0.03 (-0.24,0.19)
HD:SDS14	-0.15^b	-0.23 (-0.41,-0.05)	0.17 (-0.11,0.43)	-0.09	-0.11 (-0.28,0.08)	-0.13 (-0.35,0.09)
HDL-C						
HD:SDS12	-0.08	-0.11 (-0.27,0.05)	-0.15 (-0.41,0.13)	0.02	0.05 (-0.12,0.21)	-0.12 (-0.33,0.11)
HD:SDS14	-0.09	-0.14 (-0.30,0.03)	-0.06 (-0.32,0.22)	-0.11^b	-0.06 (-0.23,0.12)	-0.20 (-0.40,0.02)
LDL-C						
HD:SDS12	-0.17^c	-0.22 (-0.39,-0.04)	0.02 (-0.28,0.31)	-0.02	-0.09 (-0.26,0.08)	-0.00 (-0.22,0.22)
HD:SDS14	-0.14^b	-0.21 (-0.39,-0.04)	0.17 (-0.11,0.43)	-0.03	-0.11 (-0.29,0.07)	0.03 (-0.20,0.26)
IDL-C						
HD:SDS12	-0.18^c	-0.27 (-0.44,-0.09)	0.10 (-0.20,0.38)	-0.03	-0.12 (-0.28,0.05)	0.06 (-0.16,0.27)
HD:SDS14	-0.13^b	-0.23 (-0.41,-0.05)	0.24 (-0.05,0.49)	-0.05	-0.12 (-0.30,0.05)	0.06 (-0.18,0.29)
Medium HDL						
HD:SDS12	-0.12	-0.16 (-0.34,0.03)	-0.11 (-0.38,0.17)	-0.01	0.01 (-0.17,0.18)	-0.13 (-0.33,0.09)
HD:SDS14	-0.11	-0.17 (-0.35,0.02)	0.08 (-0.19,0.34)	-0.11^b	-0.07 (-0.25,0.11)	-0.12 (-0.33,0.10)
Total HDL						
HD:SDS12	-0.11	-0.15 (-0.32,0.03)	-0.15 (-0.41,0.13)	-0.01	0.02 (-0.16,0.19)	-0.13 (-0.33,0.09)
HD:SDS14	-0.11	-0.16 (-0.33,0.02)	0.03 (-0.25,0.30)	-0.13^b	-0.07 (-0.25,0.11)	-0.18 (-0.39,0.04)
Small LDL						
HD:SDS12	-0.09	-0.24 (-0.40,-0.07)	0.04 (-0.25,0.32)	-0.13^b	-0.10 (-0.27,0.07)	-0.07 (-0.28,0.15)
HD:SDS14	-0.14^b	-0.22 (-0.39,-0.05)	0.17 (-0.11,0.42)	-0.06	-0.13 (-0.30,0.05)	-0.03 (-0.25,0.19)
Medium LDL						
HD:SDS12	-0.17^c	-0.22 (-0.39,-0.05)	0.02 (-0.27,0.31)	-0.03	-0.10 (-0.26,0.07)	-0.04 (-0.25,0.18)
HD:SDS14	-0.14^b	-0.22 (-0.39,-0.04)	0.18 (-0.10,0.43)	-0.04	-0.12 (-0.29,0.06)	0.01 (-0.22,0.23)
Large LDL						
HD:SDS12	-0.19^c	-0.26 (-0.42,-0.09)	0.05 (-0.25,0.33)	-0.04	-0.12 (-0.28,0.05)	-0.01 (-0.23,0.21)
HD:SDS14	-0.15^b	-0.23 (-0.40,-0.06)	0.22 (-0.06,0.47)	-0.06	-0.14 (-0.32,0.03)	0.06 (-0.18,0.30)
Total LDL						
HD:SDS12	-0.18^c	-0.25 (-0.41,-0.08)	0.04 (-0.26,0.33)	-0.04	-0.11 (-0.27,0.06)	-0.04 (-0.25,0.18)
HD:SDS14	-0.15^b	-0.23 (-0.39,-0.06)	0.20 (-0.08,0.45)	-0.06	-0.14 (-0.31,0.04)	0.02 (-0.21,0.25)
Apolipoprotein A1						
HD:SDS12	-0.13	-0.18 (-0.35,-0.01)	-0.11 (-0.38,0.17)	0.04	0.10 (-0.10,0.30)	-0.14 (-0.36,0.10)
HD:SDS14	-0.14	-0.20 (-0.37,-0.02)	0.05 (-0.23,0.32)	-0.03	0.04 (-0.18,0.27)	-0.13 (-0.36,0.11)
Apolipoprotein B						
HD:SDS12	20.14^b	-0.20 (-0.36,-0.02)	0.09 (-0.20,0.37)	-0.03	-0.11 (-0.28,0.07)	-0.03 (-0.26,0.21)

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Females		Males	
r_P	r_A (CI)	r_P	r_A (CI)
HD:SDS14	0.04 (−0.20,0.28)	−0.08	−0.12 (−0.30,0.06)

^aPhenotypic correlations (r_P) were estimated using Pearson's correlation method. Genetic (r_A) and environmental (r_E) correlations between pubertal timing and each of the analyzed lipids and lipoproteins were obtained from the multivariate Cholesky model, which decomposes phenotypic covariation into uncorrelated genetic and environmental factors. In each multivariate model, three phenotypes were included: HD:SDS12, HD:SDS14, and one lipoprotein. CI, 95% confidence interval for r_A and r_E .

$bP < 0.05$
 $cP < 0.01$
 $dP < 0.001$.